REMARKS/ARGUMENTS

Post Final Interview.

Applicants very much appreciate the Interview with Examiner Pak and Supervisor Caputa, which occurred on Thursday, July 21, 2005. Discussions included the logic of the claim structure and the definition of certain terms, such as "cognate receptor". Ultimately, the Examiners expressed concern that the proposed amendment to claim 1 would require further investigation of the Kushner '291 reference for receptors that may be deemed cognate receptors. Applicants noted that this would be redundant because this is an issue old in the record. Applicants indicated the application would be continued in a RCE or Appeal.

The Status of the Claims.

Claims 1-13 and claim 16 are pending with entry of this amendment. Claims 1, 2 and 7 are amended herein. Claim 16 is added herein. These amendments introduce no new matter and support for the amendments is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to amended claim 1, support for the nuclear transcription factor ligand cognate receptor being other than the estrogen receptor can be found, e.g., at paragraph 14, line 6; the experiment at paragraph 123; and, the experiment at paragraph 126.

Claim 2 has been amended to merely amended to provide proper antecedent reference to a claim term.

With respect to amended claim 7, subject matter was merely removed from the claim.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

35 U.S.C. §112, Second Paragraph.

Claims 1-13 were rejected under 35 U.S.C. §112, second paragraph, for alleged lack of clarity based on the Examiner's assertion that a generic "cognate receptor" can also be an estrogen receptor. Therefore, according to the Examiner, ambiguity allegedly arose in determining if an estrogen receptor species of cognate receptor is different from an estrogen

receptor. However, this theoretical ambiguity can not exist in the current claims, as amended.

In the currently amended claim 1, the cognate receptor is not an estrogen receptor. This amendment is supported in the specification, e.g., in paragraph 14, where it is stated that "[t]he transcription factor ligand can be virtually any nuclear transcription factor ligand as long as the cell contains a cognate receptor for that ligand. It will be appreciated that the transcription factor is a factor ligand other than the compound having AP-1 mediated estrogenic activity so that the cell is in effect contacted with two different transcription factor ligands, the transcription factor ligand and the compound having AP-1 mediated estrogenic activity." Logically, this requires that the cognate receptor is other than an estrogen receptor responding to the estrogenic compound. Furthermore, the Examples section of the specification is replete with examples where the cognate receptor is not an estrogen receptor. With estrogen receptors provisoed out of the generic cognate receptor, in accordance with MPEP 2173.05(i), the cognate receptor and estrogen receptors of the claim are clearly separate entities. Therefore, Applicants request withdrawal of the section 112 rejections.

35 U.S.C. §102.

Claims 1-5 and 7-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Kushner, et al., 5,723,291. Claims 1-13 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Evans, et al., 5,639,592. Claims 1-2, 4, 8 and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Pfahl, et al., 6,004,748. Applicants traverse.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. That is, anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983). With respect to independent claim 1, and the rejected dependent claims, all limitations are not found in any of the cited references.

All limitations of claim 1 are not found in any of Kushner, Evans or Pfahl. For each of the three references, the Examiner rejected claim 1 based on a list of components of a composition allegedly found in the references. However, the claim is not to a list of

components, but a method of screening nuclear transcription factors for an ability to modulate estrogen activation at an AP-1 site. The Examiner fails to allege the presence of several components and method steps limitations required in the claims, thus failing to state a *prima facie* case. Moreover, the claims, as currently amended, plainly provide additional limitations not found in the references.

As a preliminary matter, in the Interview of July 21, 2005, the Examiner offered Kushner '291 at column 2, line 50, and column 6, line 23 to 30, as possibly describing cell systems with cognate receptors that are not estrogen receptors. Applicants note that the "mutant estrogen receptors" at column 2 are described as alternate estrogen receptors that merely have lower responses to compounds having estrogenic activity. These receptors can not provide the required limitation of a cognate receptor that is not an estrogen receptor. At column 6, two reporter constructs are described as potentially being in the same cell, but they are specifically reporter systems exclusively for estrogen responses. Again, this can not provide the missing cognate receptor limitation.

Each of the cited references essentially included a cell containing a hormone receptor (such as an estrogen receptor) that can interact with AP-1 proteins (such as fos and jun) to induce transcription of a reporter gene promoted by an AP-1 site. None of the references discuss a cognate receptor for a transcription factor ligand that is not specifically listed as being comprised in the cell of the claim. None of the references discuss contacting the cell with the transcription factor ligand which is to a cognate receptor that is not an estrogen receptor. None of the references discuss comparing expression of the reporter gene in the presence of the transcription factor ligand to expression of the reporter gene in the absence of the transcription factor ligand. Because these limitations are not present in the cited references, claim 1 and the dependent claims can not be anticipated by the references.

The Examiner alleges the "limitation of cognate receptor is generic and encompasses additional estrogen receptors or fos and jun proteins in the cell". The Examiner alleges that "both fos and jun are nuclear receptors and ligands because they are transcription factors and they bind each other." These interpretations are unreasonable in light of the specification as a whole and the plain meaning of the terms in the art. Moreover, Applicants note that claim 1, as currently amended, requires that the cognate receptor that binds the

transcription factor ligand is not an estrogen receptor. According to the Examiner's logic, if either fos or jun were considered a cognate receptor, the other would have to be considered the associated transcription factor ligand absent from the cell; however, because the claim requires both fos and jun to be present in the cell (i.e., the cell, by definition, comprises them), neither can be considered the cognate receptor or the ligand. Therefore, none of the estrogen receptor, fos, or jun can be the cognate receptor of the claims, and the cited references do not provide the required cognate receptor of the claims.

Because several required limitations are missing from the cited references, Applicants request the rejections for anticipation be withdrawn for claim 1 and all dependent claims.

Additional limitations of dependent claims are not found in the cited references. The Examiner has apparently rejected claims 2 and 3 by stating they do not further limit rejected claim 1. However, this is not the case for the claims, as amended, which include limitations not found in claim 1 and not described in the cited references. For example, with regard to claim 2, the cited references do not provide at least the limitation of a second cell comprising the cognate receptor for the nuclear transcription factor (not necessarily comprised in the first cell), or the limitation of contacting the second cell with the nuclear transcription factor ligand, or the limitation of detecting expression of a second reporter gene. With regard to claim 3, the cited references fail to provide the limitation wherein the first and second cell are the same cell.

Claims 4 and 5 were apparently rejected because they "do not further limit claim than the receptor in [rejected] claims 2 and 3." As a preliminary matter, claims 4 and 5 are not dependent on claims 2 and 3 and not required to further limit claims 2 and 3. Assuming the Examiner meant that claims 4 and 5 do not further limit rejected claim 1, the assertion is still incorrect. Claims 4 and 5 include limitations not required by claim 1 and not found in the cited art. For example, the additional limitations include at least a second cell comprising a cognate receptor of the transcription factor ligand (which is not necessarily comprised in the first cell), a response element that regulates a second reporter gene, contacting the second cell with the transcription factor ligand, and detecting the second

reporter gene. With regard to claim 5, the cited references additionally fail to provide the limitation wherein the first and second cell are the same cell.

Because many limitations of independent claim 1 and dependent claims are not present in the cited references, Applicants respectfully request the rejections for anticipation be withdrawn.

35 U.S.C. §103(a).

Claims 1-13 were rejected under 35 U.S.C. §103(a) as allegedly obvious based on Kushner in light of Pfahl, Evans, Gaub, Webb, and Kushner (WO95/06754). Applicants traverse.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure. M.P.E.P. §2143.

Specifically, a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. In re Geiger, 815 USPQ2s 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection the cited references must additionally provide a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), citing In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In the rejection, the Examiner does not point out what limitations are missing from the primary reference that are provided by the combination with all the cited art to allegedly provide all limitations of the claimed inventions. This makes the task of responding unreasonably difficult. However, in the spirit of cooperation and to expedite

prosecution, Applicants have taken reasonable efforts to evaluate the cited references against the rejected claims.

No combination of cited references provide all the limitations of any claim rejected for alleged obviousness. The cited references are cumulative and discuss essentially the same basic technology of a cell containing a hormone receptor (such as an estrogen receptor) that can interact with AP-1 proteins (such as fos and jun) to induce transcription of a reporter gene promoted by an AP-1 site. The discussion of missing limitations required to state a *prima facie* case of obviousness is essentially the same as the missing limitations arguments made above with regard to rejections based on alleged anticipation (see above). None of the references discuss the additional limitation of a cell containing an estrogen receptor and a cognate receptor for a transcription factor ligand that is not necessarily present in the cell in the presence of the listed elements (e.g., fos and jun). None of the references discuss contacting the cell with the transcription factor ligand. None of the references discuss comparing expression of the reporter gene in the presence and absence of the transcription factor ligand. Because these limitations are not present in any combination of the cited references, claim 1 and the dependent claims can not be obvious in light of any combination of the cited references.

None of the estrogen receptors, fos, or jun, can be the "cognate receptor" for the transcription factor ligand, as discussed above. Therefore, the cited references fail to provide a cell with both an estrogen receptor and a cognate receptor, as required by independent claim 1.

Again, as described above, claims 2, 3, 4, and 5, are further limiting over claim 1 and include limitations not found in the cited references. For example, Gaub, not cited as anticipating claim 1, fails for provide limitations required by the claims and not present in other cited references. Gaub provides cells comprising an estrogen receptor that on contact with external ligands induces transcription of a reporter gene through fos and jun at an estrogen responsive element. Gaub fails to provide many of the same limitations not found in Kushner, Evans or Pfahl, as discussed above. Gaub fails to provide a method of screening a nuclear transcription factor ligand for an ability to modulate estrogen activation at an AP-1 site. Gaub further fails to describe at least, e.g., a cognate receptor for a

transcription factor ligand that is not listed as comprised in the cell and which is not an estrogen receptor; contacting the cell with the transcription factor ligand to the cognate receptor; comparing expression of the reporter gene in the presence and absence of the transcription factor ligand; a second cell comprising the cognate receptor for the nuclear transcription factor (absent from the first cell); contacting the second cell with the nuclear transcription factor ligand; detecting expression of a second reporter gene; or expression of two different reporter genes in the same individual cell. The final Webb and Kushner references are admittedly cumulative and provide no additional limitations. The rejections of all claims based on alleged obviousness should be withdrawn for failure of the combined references to describe all the limitations of the claims.

The cited combinations of references are not motivated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See, *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Here, there is not suggestion in any of the references to make a combination that provides the claimed inventions. In fact, no express or implicit teaching or motivation can exist to combine references forming an invention when the references themselves do not cumulatively include all the necessary limitations of the invention.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Assuming *arguendo* that the references could provide all the limitations of any rejected claim, the suggested modification to the primary reference (Kushner) would necessarily change the principle of operation substantially. The suggested changes to the estrogen detector of Kushner (patent '291) would require a substantial reconstruction and redesign of the assay system and a change in the basic principle under which the Kushner system was designed to operate. Kushner operates, e.g., by activating AP-1 proteins to promote translation of a reporter at an AP-1 site in the presence of estrogen. With theoretical modifications to provide, e.g., claim 1, the system would have to change in

operation from a direct signal output to a new and different modulated signal output resulting from new interactions with additional receptor systems.

There would be no expectation of success in the cited combinations. Combinations of cited art would not be expected to succeed in providing the presently claimed inventions because they are missing critical limitations for the function of the screening methods.

Obviousness type Double Patenting

Claims 1-13 were also rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-27 of the '291 patent in light of Pfahl, Evans, Gaub, Webb and Kushner as indicated above. An obviousness type double patenting rejection is appropriate if the claimed invention, while not identical, is not patentably distinct with respect to the claims of a prior patent in light of the prior art. A claimed invention is not patentably distinct if all of the claimed elements are found in one or more pieces of prior art, and if there is motivation to combine the prior art with a reasonable expectation of success.

Claims 1-13 and 16 of the present invention relate to a method of screening a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site. The elements of the method are:

a) providing a first cell, in the absence of said nuclear transcription factor, comprising:

a cognate receptor for the nuclear transcription factor ligand, which cognate receptor is not an estrogen receptor;

an estrogen receptor;

fos;

jun; and,

a promoter comprising an AP-1 site that regulates expression of a first reporter gene;

b) contacting said first cell with said transcription factor ligand and with a compound having AP-1 mediated estrogenic activity; and,

c) detecting expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, wherein a

difference in expression of said first reporter gene in the presence and absence of said transcription factor ligand indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.

The '291 patent relates to a different method for screening a test compound involving providing a cell comprising: AP-1 proteins (e.g., fos and/or jun); an estrogen receptor; and, a construct comprising an AP1 site which regulates expression of a reporter gene. None of the claims of the '291 patent recites, e.g., a cell with both an estrogen receptor and a cognate receptor to an transcription factor ligand that is not fos or jun, or contacting the cell with both the transcription factor ligand to the cognate receptor and a compound having AP-1 mediated estrogenic activity, or comparing expression of a reporter gene in the presence and absence of transcription factor ligand, as is found in independent claim 1 of the present invention. Additional limitations not found in the specification of the '291 patent, as discussed above, are also not present in the '291 claims.

The Examiner has not pointed to anything in the cited references that provides the limitations missing from the rejected claims. Applicants have not found these limitations with reasonable efforts. The cited references cumulatively provide, e.g., hormone receptors that activate expression of a reporter gene through an AP-1 protein/receptor element pathway. As discussed above in the arguments against the obviousness rejections, no combination of the same cited references provides any of several limitations including, e.g., a method of screening a nuclear transcription factor ligand, which binds cognate non-estrogen receptor to modulate estrogen activation of an AP-1 site.

The present claims are patentably distinct from the '291 claims because many of the claimed elements are not found in the suggested combination of references. Furthermore, there is no motivation to combine the prior art with a reasonable expectation of success, as discussed above. Therefore, the rejection for alleged double patenting should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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Respectfully submitted,

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Attachments:

1) A transmittal sheet;
2) A fee transmittal sheet;
3) A Request for Continued Examination;
4) A Request for a 2-month Extension; and,
5) A receipt indication postcard.

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